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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
05213-0730 (43170-219693)

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on November 9, 2005

Signature

Typed or printed name Robert E. Richards

Application Number	Filed
09/641,327	August 18, 2000

First Named Inventor
AGOSTON ET AL.

Art Unit	Examiner
1616	S.N. Qazi, Ph.D.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record. Registration number 29,105

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

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November 9, 2005
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
GREGORY E. AGOSTON, ET AL.	)	
	)	
Serial No.: 09/**08/641,327**	)	**Art Unit:** 1616
	)	
Filed: **August 18, 2000**	)	**Examiner:** S. N. Qazi, Ph.D.
	)	
For: **ANTIANGIOGENIC AGENTS**	)	

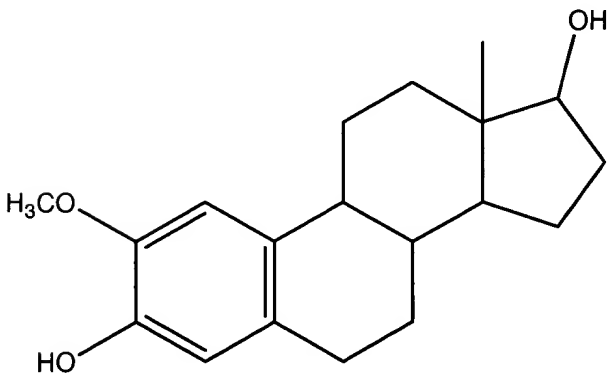
ATTACHMENT TO PRE-APPEAL BRIEF REQUEST FOR REVIEW

Summary of Argument

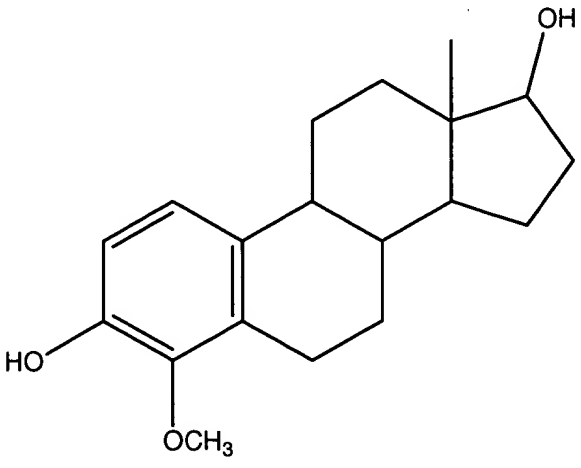
The rejection by the examiner under 35 U.S.C. §103(a) is improper because (1) the art of estradiols is highly unpredictable; and (2) the examiner failed to consider the teachings of the prior art as a whole.

The Art Of Estradiols Is Highly Unpredictable

Applicants submit that the art of estradiols is highly unpredictable. The change of a single substituent from one ring position to another ring position can change the properties of the compound from being antiangiogenic to carcinogenic. For example, 2-methoxyestradiol is antiangiogenic, while 4-methoxyestradiol is mutagenic or carcinogenic. The structures of these compounds is shown below.



2-Methoxyestradiol



4-Methoxyestradiol

The only difference between the two foregoing compounds is whether the methoxy group is at the 2-position or the 4-position of the A-ring. This difference clearly demonstrates that estradiol derivatives and analogs are highly unpredictable in their properties.

Therefore, applicants disagree that the properties of homologues of 2-methoxyestradiol are expected by those skilled in the art to be the same as that of 2-methoxyestradiol. The examiner apparently acknowledges this fact by stating, "Considering the unpredictability the claimed method of treating angiogenesis having various substituents at 16-position would not be obvious to one skilled in the art." Office Action dated 8/11/2005 at page 2. However, the examiner then rejects Claim 39 as being structurally similar to 2-methoxyestradiol when R_{h1} and/or R_{h2} are methyl or ethyl based solely on alleged homology. This rejection ignores the undisputed proposition that the art of estradiols is highly unpredictable and the object of the present invention.

The objective of the invention is to reduce the rate of metabolism of the compound to a less desirable form. Applicants have unexpectedly discovered that if the 16-position is substituted, as presently claimed, the 16-position substituents provide steric bulk which reduces that rate at which the 17-position hydroxyl group is metabolized, thereby prolonging the active life of the compound.

The prior art relied upon by the examiner fails to appreciate the problem of metabolism of 2-methoxyestradiol to a less desirable form, such as 2-methoxyestrone. By the failure of those skilled in the art to appreciate this metabolism problem, it cannot be said that substitution of the 16-position, as claimed, would have been obvious to the skilled artisan. There is no motivation in the art to substitute the 16-position in preference to substituting the 15-position, the 14-position, the 13-position, etc. It is the selection of the 16-position for substitution, as claimed, which is unobvious.

Respectfully, Applicants submit that a showing of *prima facie* obviousness has not been established by the Examiner because, among other reasons, the cited art does not teach or suggest the problem nor the solution of the problem which Applicants have identified. *See In re Peehs*, 612 F.2d 1287, 204 USPQ 835 (CCPA 1980); *In re Zurcko* 111 F.3d 887, 42 USPQ2d 1476 (Fed. Cir. 1997).

Applicants recognized and identified the problems of 2-methoxyestradiol being metabolized to the much less active metabolite 2-methoxyestrone, *and* being deactivated by an additional metabolic deactivation pathway that results in the glucuronidation of 2-methoxyestradiol. *See* specification page 9, line 24--page 10, line 9. To solve this problem, Applicants' invention *adds steric bulk and/or modification of electrostatic characteristics at the 16-carbon* of 2-methoxyestradiol, to retard or prevent interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate. *Id.* Further, the addition of steric bulk and/or electrostatic modification at the 16-carbon may retard or prevent glucuronidation. *Id.* It is believed that retardation or prevention of these two metabolic deactivation pathways prolongs the serum lifetime of 2-methoxyestradiol and other estrogenic compounds while retaining the desired anti-angiogenic and anti-tumor activity. *Id.* Indeed, initial screening of epimeric 16-ethyl-2-methoxyestradiol and related analogues showed that it is about equipotent to 2-methoxyestradiol in inhibition of HUVEC cell proliferation *in vitro*. However, since 16-ethyl-2-methoxyestradiol is not metabolized as quickly as 2-methoxyestradiol *in vivo*, it has a longer period of time to be active, and, therefore, more effective.

None of the prior art of record discloses, and EntreMed Overview and Attala et al. do not disclose the problem discovered by applicants; *i.e.*, deactivation of the anti-angiogenic effects of estradiol derivatives by metabolic processes. In the absence of an appreciation of the problem, the solution of the problem is clearly nonobvious.

The Rejection Failed To Consider The Prior Art As A Whole

Furthermore, Section 2144.09 of the MPEP discusses the subject of close structural similarity between chemicals. The MPEP makes it clear that even if compounds are homologous, homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed "as a whole." MPEP §2144.09. Thus, it would be erroneous for the examiner to contend that the present claims are *prima facie* obvious merely because of alleged homology or structural similarity. The examiner must consider the claimed invention and the prior art as a whole in making a determination of alleged obviousness. Thus, the problem of deactivation discovered by applicants and the solution of that problem by substituting estradiols at the 16-position to provide bulk hindrance to deactivation mechanisms must also be considered.

To illustrate how the claimed invention and the prior art must be considered as a whole, the MPEP discusses the case of *In re Langer*, 465 F.2d 896 (CCPA 1972). The MPEP states, "Claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from the claimed amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class." MPEP §2144.09.

The same principal of law is applicable in the present case. In the present case the prior art does not disclose sterically hindering degradation of the hydroxyl group substituted at the 17-position by using bulk-hindering substituents substituted at the 16-position. Therefore, the prior art fails to teach the concept of using bulk hindrance at the 16-position to protect against anti-angiogenic deactivation of the claimed estradiol derivatives.

Conclusion

The MPEP states that, "The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (appellant produced sufficient evidence to establish a substantial degree of unpredictability in the pertinent art area, and thereby rebutted the presumption that structurally similar compounds have similar properties)." MPEP §2144.09. Applicants submit that the foregoing showing of unpredictability and lack of appreciation of the problem by the prior art as a whole overcomes any alleged *prima facie* obviousness of the presently claimed compounds.

Applying the rulings of the CCPA (the predecessor court of the Federal Circuit) in *In re Langer* and *In re May* to the facts of the present case and considering the prior art and the claimed invention as a whole dictates a finding of nonobviousness of the presently claimed invention. Therefore, the rejection of the Claim 39 under 35 U.S.C. § 103(a) as being obvious in view of the prior art of record is improper and should be reversed.